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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 209/48, A61K 31/40 — A1

(11) International Publication Number: WO 96/20926

(43) International Publication Date: 11 July 1996 (11.07.96)

(21) International Application Number: PCT/US95/15384

(22) International Filing Date: 20 November 1995 (20.11.95)

(30) Priority Data:
08/366,679 30 December 1994 (30.12.94) US

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(81) Designated States: AU, CA, CZ, FI, HU, JP, KR, NZ, PL, RU, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SUBSTITUTED IMIDES AS TNF INHIBITORS

(57) Abstract

Novel imides are inhibitors of tumor necrosis factor α and can be used to combat cachexia, endotoxic shock, and retrovirus replication. A typical embodiment is 2-Phthalimido-3-(3',4'-dimethoxyphenyl)propane.

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SUBSTITUTED IMIDES AS TNF INHIBITORS

Background of the Invention

The present invention relates a method of reducing levels of TNFα in a mammal and to compounds and compositions useful therein.

TNFα, or tumor necrosis factor α, is a cytokine which is released primarily by mononuclear phagocytes in response to various immunostimulators. When administered to animals or humans it causes inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase responses similar to those seen during acute infections and shock states.

Excessive or unregulated TNFα production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome {Tracey *et al.*, *Nature* 330, 662-664 (1987) and Hinshaw *et al.*, *Circ. Shock* 30, 279-292 (1990)}; cachexia {Dezube *et al.*, *Lancet*, 335(8690), 662 (1990)}; and Adult Respiratory Distress Syndrome where TNFα concentration in excess of 12,000 pg/milliliters have been detected in pulmonary aspirates from ARDS patients {Millar *et al.*, *Lancet* 2(8665), 712-714 (1989)}. Systemic infusion of recombinant TNFα also resulted in changes typically seen in ARDS {Ferrai-Baliviera *et al.*, *Arch. Surg.* 124(12), 1400-1405 (1989)}.

TNFα appears to be involved in bone resorption diseases, including arthritis where it has been determined that when activated, leukocytes will produce a bone-resorbing activity, and data suggest that TNFα contributes to this activity. {Bertolini *et al.*, *Nature* 319, 516-518 (1986) and Johnson *et al.*, *Endocrinology* 124(3), 1424-1427 (1989).} It has been determined that TNFα stimulates bone resorption and inhibits bone formation *in vitro* and *in vivo* through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNFα may be involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNFα by tumor or host tissues and malignancy associated hypercalcemia {*Calci. Tissue Int. (US)* 46(Suppl.), S3-10 (1990)}. In Graft versus Host Reaction, increased serum

TNFα levels have been associated with major complication following acute allogenic bone marrow transplants {Holler *et al.*, *Blood*, 75(4), 1011-1016 (1990)}.

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNFα and the most severe complication occurring in malaria patients. Levels of serum TNFα correlated directly with the severity of disease and the prognosis in patients with acute malaria attacks {Grau *et al.*, *N. Engl. J. Med.* 320(24), 1586-1591 (1989)}.

TNFα also plays a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibody to TNFα completely blocked the silica-induced lung fibrosis in mice {Pignet *et al.*, *Nature*, 344:245-247 (1990)}. High levels of TNFα production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis {Bissonnette *et al.*, *Inflammation* 13(3), 329-339 (1989)}. Alveolar macrophages from pulmonary sarcoidosis patients have also been found to spontaneously release massive quantities of TNFα as compared with macrophages from normal donors {Baughman *et al.*, *J. Lab. Clin. Med.* 115(1), 36-42 (1990)}.

TNFα is also implicated in the inflammatory response which follows reperfusion, called reperfusion injury, and is a major cause of tissue damage after loss of blood flow {Vedder *et al.*, *PNAS* 87, 2643-2646 (1990)}. TNFα also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin {Sherry *et al.*, *J. Cell Biol.* 107, 1269-1277 (1988)}. TNFα has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNFα-induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells {Munro *et al.*, *Am. J. Path.* 135(1), 121-132 (1989)}.

Moreover, it now is known that TNFα is a potent activator of retrovirus replication including activation of HIV-1. {Duh *et al.*, *Proc. Nat. Acad. Sci.* 86, 5974-5978 (1989); Poll *et al.*, *Proc. Nat. Acad. Sci.* 87, 782-785 (1990); Monto *et al.*, *Blood* 79, 2670 (1990); Clouse *et al.*, *J. Immunol.* 142, 431-438 (1989); Poll *et al.*, *AIDS Res. Hum. Retrovirus*, 191-197 (1992)}. AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, *i.e.*, HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNFα, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNFα, in an HIV-infected individual aids in limiting the maintenance of T lymphocyte caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. {Rosenberg *et al.*, *The Immunopathogenesis of HIV Infection*, Advances in Immunology, 57 (1989)}. Cytokines, such as TNFα, have been shown to activate HIV replication in monocytes and/or macrophages {Poli *et al. Proc. Natl. Acad. Sci.*, 87, 782-784 (1990)}, therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression as stated above for T cells. Additional studies have identified TNFα as a common factor in the activation of HIV *in vitro* and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, *et al.*, *PNAS*

86, 2336-2340). This evidence suggests that a reduction of TNFα synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNFα {Folks *et al.*, *PNAS* 86, 2365-2368 (1989)}. A molecular mechanism for the virus inducing activity is suggested by TNFα's ability to activate a gene regulatory protein (NFκB) found in the cytoplasm of cells, which promotes HIV replication through binding to a viral regulatory gene sequence (LTR) {Osborn *et al.*, *PNAS* 86, 2336-2340 (1989)}. TNFα in AIDS and cancer associated cachexia is suggested by elevated serum TNFα and high levels of spontaneous TNFα production in peripheral blood monocytes from patients {Wright *et al. J. Immunol.* 141(1), 99-104 (1988)}. Eur J. Gastroen Hepat 6(9), 821-829, 1994.

TNFα has been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

Preventing or inhibiting the production or action of TNFα is, therefore, predicted to be a potent therapeutic strategy for many inflammatory, infectious, immunological or malignant diseases. These include but are not restricted to septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury. Efforts directed to the suppression of the effects of TNFα have ranged from the utilization of steroids such as dexamethasone and prednisolone to the use of both polyclonal and monoclonal antibodies {Beutler *et al.*, *Science* 234, 470-474 (1985); WO 92/11383}. (Clinical and Experimental Rheumatology 1993, 11 (Suppl. 8), 5173-5175). (PNAS 1992, 89, 9784-88). (Annals of the Rheumatic Diseases 1990, 49, 480-486).

The nuclear factor κB (NFκB) is a pleiotropic transcriptional activator (Lenardo, *et*

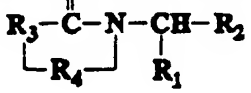
al. Cell 1989, 58, 227-29). NFκB has been implicated as a transcriptional activator in a variety of disease and inflammatory states and is thought to regulate cytokine levels including but not limited to TNFα and also to be an activator of HIV transcription (Dbaibo, *et al.* J. Biol. Chem. 1993, 17762-66; Duh *et al.* Proc. Natl. Acad. Sci. 1989, 86, 5974-78; Bachelerie *et al.* Nature 1991, 350, 709-12; Boswas *et al.* J.. Acquired Immune Deficiency Syndrome 1993, 6, 778-786; Suzuki *et al.* Biochem. And Biophys. Res. Comm. 1993, 193, 277-83; Suzuki *et al.* Biochem. And Biophys. Res Comm. 1992, 189, 1709-15; Suzuki *et al.* Biochem. Mol. Bio. Int. 1993, 31(4), 693-700; Shakhov *et al.* 1990, 171, 35-47; and Staal *et al.* Proc. Natl. Acad. Sci. USA 1990, 87, 9943-47). Thus, inhibition of NFκB binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms be useful in the inhibition of a multitude of disease states. The compounds claimed in this patent can inhibit the action of NFκB in the nucleus and thus are useful in the treatment of a variety of diseases including but not limited to rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, other arthritic conditions, septic shock, septis, endotoxic shock, graft versus host disease, wasting, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, HIV, AIDS, and opportunistic infections in AIDS.

TNFα and NFκB levels are influenced by a reciprocal feedback loop. As noted above, the compounds of the present invention affect the levels of both TNFα and NFκB. It is not known at this time, however, how the compounds of the present invention regulate the levels of TNFα, NFκB, or both.

Detailed Description

The present invention is based on the discovery that a class of non-polypeptide imides more fully described herein appear to inhibit the action of TNFα.

The present invention pertains to compounds of the formula:



(I)

in which:

R^1 is (*i*) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (*ii*) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, straight or branched alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iii) benzyl or benzyl substituted with ne or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, or (iv) -Y-Ph where Y is a straight, branched, or cyclic alkyl of 1 to 12 carbon atoms and Ph is phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo;

R^2 is -H, a branched or unbranched alkyl of 1 to 10 carbon atoms, phenyl, pyridyl, heterocycle, $-CH_2$-Aryl, or $-CH_2$-heterocycle;

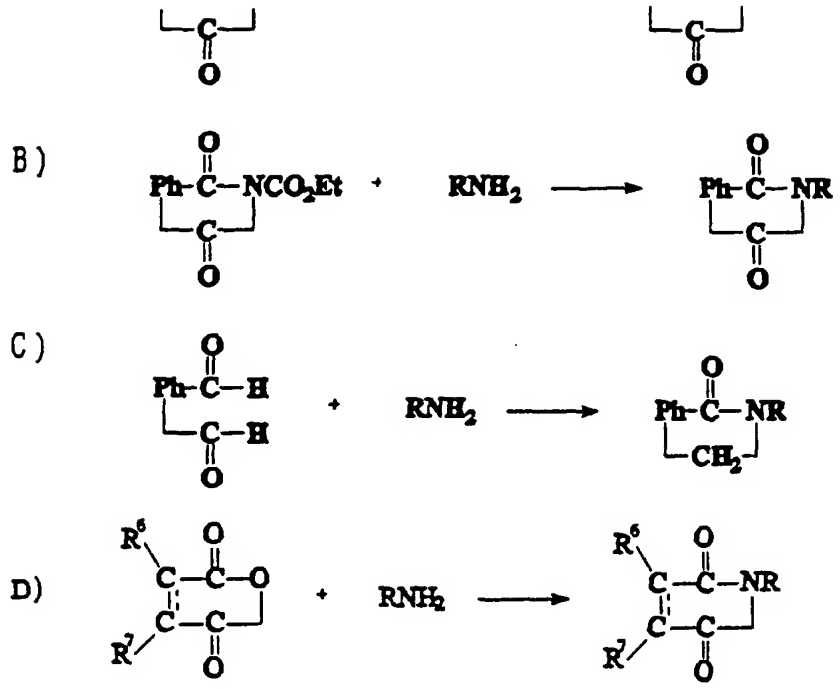
R^3 is i) ethylene, ii) vinylene, iii) a branched alkylene of 3 to 10 carbon atoms, iv) a branched alkenylene of 3 to 10 carbon atoms, v) cycloalkylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro,

cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, vi) cycloalkenylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or vii) *o*-phenylene unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; and,

R^4 is -CX, or $-CH_2-$;
X is O or S.

The term alkyl as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and the like. When qualified by "lower", the alkyl group will contain from 1 to 6 carbon atoms. The same carbon content applies to the parent term "alkane" and to derivative terms such as "alkoxy".

The compounds can be prepared using methods which are known in general for the preparation of imides. General reaction schemes include the reaction of the substituted amine with either phthalic anhydride, N-carbethoxyphthalimide, 1,2-benzenedicarbaldehyde or various substituted anhydrides as illustrated by the formulas:



R is $-\underset{\displaystyle R^1}{\overset{|}{C}}H-R_2$

R^6 and R^7 are hydrogen, nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, halo or R^6 and R^7 together with the carbons to which they are attached represent a cycloalkylene ring of 4 to 9 carbon atoms unsubstituted or substituted with one or more substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl,

acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo.

A first preferred subclass of Formula I pertains to compounds in which:
R^1 is 3,4-diethoxyphenyl and 3,4-dimethoxyphenyl
R^3 is *o*-phenylene substituted with amino; and,
R^4 is -CO- or $-CH_2-$:

The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNFα. The compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20-100 milligrams/milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 500 milligrams/day as needed in single or multiple daily administration. In general, an initial treatment regimen can be copied from that known to be effective in interfering with TNFα activity for other TNFα mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia such as levels of reverse transcriptase or viral proteins, and/or for progression of cytokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is found following the normal treatment regimen, then the amount of cytokine activity interfering agent administered is increased, *e.g.*, by fifty percent a week.

The compounds of the present invention also can be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNFα production, respectively, such as viral infections, such as those caused by the herpes viruses, or viral conjunctivitis, *etc.*

The compounds also can be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNFα production. TNFα mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

Certain of these compounds possess centers of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both of the resolved bases, optionally repeating the process, so as to obtain either or both substantially free of the other; *i.e.*, in a form having an optical purity of >95%.

Prevention or inhibition of production of TNFα by these compounds can be conveniently assayed using anti-TNFα antibodies. For example, plates (Nunc Immunoplates, Roskilde, DK) are treated with 5 μg/milliliter of purified rabbit anti-TNFα antibodies at 4°C for 12 to 14 hours. The plates then are blocked for 2 hours at 25°C with PBS/0.05% Tween containing 5 milligrams/milliliter BSA. After washing, 100 μL of unknowns as well as controls are applied and the plates incubated at 4°C for 12 to 14 hours. The plates are washed and assayed with a conjugate of peroxidase (horseradish) and mouse anti-TNFα

monoclonal antibodies, and the color developed with *o*-phenylenediamine in phosphate-citrate buffer containing 0.012% hydrogen peroxide and read at 492 nm.

Typical compounds of this invention include:

1-phthalimido-1-(3',4'-diethoxyphenyl)ethane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)ethane,
1-phthalimido-1-(3',4'-diethoxyphenyl)propane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)propane,
1-phthalimido-1-(3',4'-diethoxyphenyl)butane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)butane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-2-phenylethane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-2-phenylethane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-3-pyridylpropane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-3-pyridlpropane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-3-phenylpropane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-3-phenylpropane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-2-pyridylethane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-2-pyridylethane,
1-phthalimido-1-(3',4'-diethoxyphenyl)butane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)butane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-2-imidazolylethane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-2-imidazolylethane,
1-phthalimido-1-(3',4'-diethoxyphenyl)-3-methylbutane,
1-(1'-oxoisoindolinyl)-1-(3',4'-diethoxyphenyl)-3-methylbutane.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1

2-Phthalimido-3-(3,4-dimethoxyphenyl)propane. To a stirred solution of 3-(3,4-dimethoxyphenyl)-2-aminopropane (1.95 grams, 10.0 mmol) and sodium carbonate (1.06 grams, 10.0 mmol) in 50 milliliters of water was added N-carbethoxyphthalimide (2.19 grams, 10.0 mmol). After 10 minutes the reaction mixture was diluted with 40 milliliters of acetonitrile and the mixture stirred for 40 minutes The reaction solution was partially concentrated in vacuo to remove the acetonitrile. The resulting mixture of an oil and aqueous layer was extracted with methylene chloride (25 milliliters). The organic extract was dried over sodium sulfate and concentrated in vacuo to afford a crude product which was purified by flash chromatography to afford 1.73 grams (53%) of product as a thick oil which slowly solidified to a white wax: ^{1}H NMR (dmso-d_6, 250 MHz) δ 7.7 (m, 4 H, Ar), 6.7 (m, 3 H, Ar), 4.63 (m, 1 H, CH), 3.79 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 3.28 (dd, 1 H, J = 13.8, 9.8 Hz), 3.03 (dd, J = 13.8, 6.5 Hz, 1 H), 1.54 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (dmso-d_6) δ 168.4, 148.6, 147.4, 133.7, 131.8, 130.9, 122.9, 120.9, 111.1, 55.7, 55.6, 48.6, 39.3, 18.3. Anal. Calcd for $C_{19}H_{19}NO_2$. Theoretical C, 70.14; H, 5.89; N, 4.30. Found C, 70.08; H, 5.83; N, 4.30.

Example 2

1-Phthalimido-1-(3', 4'-dimethoxyphenyl)ethane.

a) 3',4'-Dimethoxyacetophenone oxime. A solution of hydroxylamine hydrochloride (3.33 grams, 48 mmol) and sodium acetate (4.92 grams, 60 mmol) in 20 milliliters of water was added to a stirring solution of 3',4'-dimethoxyacetophenone (5.41 grams, 30.0 mmol) in a mixture of water (30 milliliters) and ethanol (30 milliliters), the solution was stirred overnight. The resulting mixture was filtered and the solid was dried *in vacuo* (60 °C , < 1mm) to afford 4.68 grams (80%) of product as a yellow solid: mp 137-138 °C ; ^{1}H NMR ($CDCl_3$) δ 7.34-7.08 (m , 2H), 6.94-6 80 (m , 1H), 3.92 (s , 3H), 3.90 (s , 3H), 2.28 (s , 3H) ; ^{13}C NMR ($CDCl_3$) δ 155.6, 150.1, 148.8, 129.2, 119.2, 110.6, 108.6, 55.8.

b) **1-(3',4'-Dimethoxyphenyl)ethylamine.** 3',4'-Dimethoxyacetophenone oxime (1 gram, 5.1 mmol) was dissolved in 10 milliliters of glacial acetic acid, the solution was flushed with N_2 and the palladium on carbon (0.2 grams, 5%) was added. The mixture was treated with 60 psi of H_2 in a Parr Type Shaker for 24 hours. The catalyst was filtered off and the filtrate was concentrated to afford a yellow oil which was taken up in water, basified to pH 12 with a saturated solution of sodium carbonate and extracted with methylene chloride. The combined extracts were dried over magnesium sulfate and concentrated to afford 1.97 grams (82%) of product as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.02-6.75 (m , 3H), 4.08 (q , J_1 = 6.6Hz , J_2 = 13.1Hz , 1H), 3.89 (s , 3H), 3.87 (s , 3H), 1.37 (d , J = 6.6Hz , 3H).

c) **1-Phthalimido-1-(3', 4'-dimethoxyphenyl)ethane.** To a stirred solution of 1-(3',4'-dimethoxyphenyl)ethylamine (1.81 grams, 10.0 mmol) and sodium carbonate (1.14 grams, 10.8 mmol) in a mixture of water (80 milliliters) and acetonitrile (50 milliliters) was added N-carbethoxyphthalimide (2.19 grams, 10 mmol). The resulting suspension was stirred for 3.5 hours at room temperature and then filtered to afford 1.24 grams (40%) of crude product as a white powder. The crude product was recrystallized from hexane/ethyl acetate and dried *in vacuo* (60 °C , < 1mm) to afford 0.85 grams (27%) of the product as white crystals: mp 124 - 125 °C ; ^{1}H NMR (DMSO-d_6) δ 7.96-7.78 (m , 4H), 7.09-6.81 (m , 3H), 5.40 (q , J = 7.2Hz , 1H), 3.73 (s , 3H), 3.72 (s , 3H), 1.81 (d , J = 7.2Hz , 3H) ; ^{13}C NMR (DMSO-d_6) δ 167.6, 148.4, 148.0, 134.4, 132.9, 131.3, 122.9, 118.8, 111.5, 110.8, 55.4, 48.6, 17.7. Anal. Calculated for $C_{18}H_{17}NO_4$. Theoretical : C , 69.44 ; H , 5.50 ; N , 4.50. Found : C, 69.63 ; H , 5.45 ; N , 4.42. HPLC 100%.

Example 3

1-Phthalimido-1-(4'-methoxyphenyl)propane.

a) **4'-Methoxypropiophenone oxime.** A solution of hydroxylamine hydrochloride (3.33 grams, 48 mmol) and sodium acetate (4.92 grams, 60 mmol) in 20 milliliters of water was added to a stirred solution of 4-methoxypropiophenone (5.26 grams, 30.0 mmol) in a

mixture of water (30 milliliters) and ethanol (30 milliliters), a further 20 milliliters of ethanol was added to get a homogenous solution, which was stirred overnight. The resulting slurry was filtered, the filtrate was partially concentrated, to remove the ethanol and a white solid precipitated. The slurry was filtered and the solid was washed with water, and dried *in vacuo* (25 °C , < 1 mm) to afford 5.26 grams (98%) of product as a white solid : ^{1}H NMR ($CDCl_3$) δ 7.64-7.42 (m , 2H), 7.04-6.81(m , 2H), 3.82(s , 3H), 2.81(q , J = 7.6Hz , 2H), 1.17(t , J = 7.6Hz, 3H).

b) 1-(4'-Methoxyphenyl)propylamine. To a N_2 flushed solution of 4'-methoxypropiophenone oxime (4 grams, 22.3 mmol) in glacial acetic acid (40 milliliters) was added 0.8 grams of 5% Pd/C. The mixture was treated with 60 psi of H_2 in a Parr Type Shaker for 23 hours. The catalyst was filtered off through celite and the filtrate was concentrated to afford a yellow oil. The oil was taken up in water, the pH was adjusted to 12 using a saturated solution of sodium carbonate, and extracted with methylene chloride. The organic extract was dried over magnesium sulfate and concentrated to afford 3.04 grams (83%) of product as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.32-7.20(m , 2H), 6.94-6.82(m , 2H), 3.79(s , 3H), 1.88-1.54(m , 4H), 0.87(t , J = 7.4Hz , 3H).

c) 1-Phthalimido-1-(4'-methoxyphenyl)propane. To a stirred solution of 1-(4'-methoxyphenyl)propylamine (2.5 grams, 15.2 mmol) and sodium carbonate (1.74 grams, 16.4 mmol) in a mixture of water (50 milliliters) and acetonitrile (50 milliliters) was added N-carbethoxyphthalimide (3.34 grams, 15.2 mmol). The resulting suspension was stirred for 4.5 hours at room temperature, the acetonitrile was removed in vacuo and a solid formed. The slurry was filtered and the solid was washed with water and air dried to afford 1.73 grams (39%) of crude product as a white powder. The crude product was recrystallized from hexane/ethyl acetate and dried *in vacuo* (60 °C, < 1 mm) to afford 1.71 grams (38%) of the product as white crystals: mp 85-86 °C ; ^{1}H NMR (DMSO-d_6) δ 7.92-7.79(m , 4H), 7.46-7.28(m , 2 H), 6.97-6.83(m , 2 H), 5.19-5.06(m , 1 H), 3.72(s , 3H), 2.56-2.13(m , 2 H), 0.87(t

, J = 7.3Hz , 3 H) ; ^{13}C NMR (DMSO-d_6) δ 167.8, 1 .5, 134.6, 131.7, 131.0, 128.6, 123.1, 113.7, 55.2, 54.9, 23.8, 11.3. Anal. Calculated for $C_{18}H_{17}NO_3$. Theoretical : C ,73.20; H , 5.80 ; N , 4.74. Found : C,73.24; H , 5.74 ; N , 4.86. HPLC 100%.

Example 4

1-Phthalimido-1-(3',4'-dimethoxyphenyl)methane. To a stirred solution of 3,4-dimethoxybenzylamine (0.836 grams, 5.00 mmol) and N-carbethoxyphthalimide (1.10 grams, 5.00 mmol) in 20 milliliters of tetrahydrofuran was added 1 drop of triethylamine and the mixture stirred overnight. After 24 hours at room temperature, the mixture was refluxed for 16 hours, then allowed to cool to room temperature without stirring. Crystals formed on cooling. The mixture was filtered, the solid dried in vacuo to afford 0.89 grams (60%) of 1-phthalimido-1-(3',4'-dimethoxyphenyl)methane as small white needles: mp 160-161 °C; ^{1}H NMR ($CDCl_3$/TMS) δ 7.8 (m, 2 H), 7.7 (m, 2 H), 7.03 (m, 2 H), 6.8 (m, 1 H), 4.78 (s, 2 H), 3.88 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$/TMS) δ 168.0, 148.9, 148.7, 133.9, 132.1, 129.0, 123.3, 121.3, 112.1, 111.1, 55.9, 41.4. Anal. Calcd for $C_{17}H_{15}NO_4$. Theory C, 68.68; H, 5.09; N, 4.71. Found C, 68.49; H, 4.99; N, 4.67.

Example 5

1-Phthalimido-(3,4-dimethoxyphenyl)toluene.

a) **1-Phenyl-1-(3,4-dimethoxyphenyl)methylamine.** To a stirring solution of 3,4-dimethoxybenzonitrile (1.63 grams, 10.0 mmol) in tetrahydrofuran (25 milliliters) was added phenyl magnesium bromide (3.7 milliliters , 3M , 11.0 mmol) and the resulting solution was refluxed for 40 minutes. The progress of the reaction was monitored by TLC (30% ethyl acetate/methylene chloride, UV), after 40 minutes the reaction was complete. The reaction mixture was allowed to cool and methanol (25 milliliters) was added slowly. When the effervescence had ceased sodium borohydride (0.40 grams, 10.5 mmol) was added slowly and

the reaction mixture was stirred at room temperature overnight. The resulting dark purple mixture was extracted with ether (3 times with 50 milliliters) and the combined ether extracts back extracted into aqueous 3N hydrochloric acid (150 milliliters). The pH of the aqueous layer was then adjusted to 14 using sodium hydroxide (5 Molar) and the mixture was extracted with methylene chloride (2 times with 50 milliliters). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo* to afford 1.76 grams (72%) of product as an orange oil ; ^{1}H NMR ($CDCl_3$) δ 7.43-7.16(m , 5H), 6.95-6.74(m , 3H), 5.17(s , 1H), 3.85(s , 3H), 3.84(s , 3H), 1.78(s , 2H).

b) A mixture of 1-phenyl-1-(3,4-dimethoxyphenyl)methylamine (0.73 grams, 3 mmol) and phthalic anhydride (0.44 grams, 3 mmol) were melted together and stirred for 5 minutes. After cooling, 1 gram of crude product formed as a yellow/orange glassy solid. The crude product was recrystallized from toluene and dried *in vacuo* (60°C , < 1 mm) to afford 0.36g (33%) of product as a white solid ; ^{1}H NMR (DMSO-d_6) δ 12.96(s , 1H), 9.31-9.17(m , 1H), 7.85-6.73(m , 12H), 6.42-6.22(m , 1H), 3.72(s , 6H) ; ^{13}C NMR (DMSO-d_6) δ 167.7, 167.6, 148.5, 147.6, 142.7, 138.5, 134.8, 131.2, 130.5, 129.1, 128.9, 128.1, 127.8, 127.3, 126.6, 119.6, 111.5, 111.4, 55.7, 55.4, 55.4.

c) 1-Phthalimido-(3,4-dimethoxyphenyl)toluene. A solution of the product of step b) above (0.25 grams, 0.68 mmol) and sodium acetate (0.03 grams, 0.34 mmol) in acetic anhydride (6 milliliters) was refluxed for 30 minutes. The progress of the reaction was monitored by TLC (2 % ethyl acetate/methylene chloride , UV) and reached completion after 30 minutes. The reaction mixture was cooled to room temperature, poured into iced water (20 milliliters) and stirred for 15 minutes. The mixture was extracted into methylene chloride (25 milliliters) and was washed successively with a saturated aqueous solution of sodium bicarbonate (15 milliliters), brine (10 milliliters), sodium bicarbonate (15 milliliters) and brine (10 milliliters). The organic layer was dried over magnesium sulfate and

concentrated *in vacuo* to afford 0.19 grams of crude product as a orange oil. The crude product was purified by flash chromatography (silica gel , 10% ethyl acetate/methylene chloride) and dried *in vacuo* (25°C , < 1 mm) to afford 0.15 grams (63%) of product as a slightly green colored solid: ^{1}H NMR ($CDCl_3$) δ 7.90-7.64(m , 4 H), 7.39-7.22(m , 5H), 7.07-6.91(m , 2 H), 6.88-6.76(m , 1 H), 6.66(s , 1 H), 3.87(s , 3 H), 3.80(s , 3 H) ; ^{13}C NMR ($CDCl_3$) δ 167.9, 148.8, 148.6, 138.3, 134.1, 131.9, 130.8, 128.3, 128.1, 127.5, 123.4, 121.6, 112.5, 110.7, 57.6, 55.9, 55.8.

Example 6

1-Phthalimido-1-(3',4'-dimethoxyphenyl)pentane

a) **3',4'-Dimethoxyvalerophenone.** 3',4'-Dimethoxyacetophenone (9.91 grams, 55 mmol) was added over 20 minutes to a cooled (0°C) stirred solution of lithium diisopropylamide (28.9 milliliters, 2M, 57.8 mmol). After an additional 5 minutes the solution was cooled to -78°C and 1-iodopropane (10.73 milliliters, 110 mmol) was rapidly added. The solution was allowed to slowly warm to room temperature and stirring was continued for 3 days. Reaction progress was monitored by TLC (30%, ethyl acetate/ hexane, UV) and an equilibrium had been reached after three days between starting material (Rf = 0.15), monoalkylated product (Rf = 0.32) and dialkylated product (Rf = 0.42). The reaction was treated with water (60 milliliters), ethyl acetate (100 milliliters) and a saturated solution of sodium bicarbonate (100 milliliters). The organic layer was separated and washed successively with 5% hydrochloric acid (100 milliliters) and saturated aqueous sodium bicarbonate (100 milliliters). The organic layer was dried over magnesium sulfate and concentrated to afford 15.17 grams of crude product as an orange oily liquid. The crude product was purified by flash chromatography (silica gel , 20% ethyl acetate/hexane) to afford 3.68 (25%) of the dialkylated product (3',4'-dimethoxy-2-propylvalerophenone) as a yellow solid and 1.01 grams (8%) of the monoalkylated product (3',4'-dimethoxyvalerophenone) as a yellow oily liquid: ^{1}H NMR ($CDCl_3$) δ 7.65-7.50(m , 2H), 6.95-6.85(m , 1H), 3.95(s , 3 H), 3.94(s , 3 H), 2.99-2.88(m , 2 H), 1.81-1.64(m , 2 H), 1.52-

1.34(m , 2 H), 1.04-0.91(m , 3 H). ^{13}C NMR ($CDCl_3$) δ 199.1, 152.9, 148.8, 130.2, 122.5, 110.0, 109.8, 55.9, 55.8, 37.7, 26.7, 22.4, 13.8.

b) 3',4'-Dimethoxyvalerophenone oxime.

To a stirred solution of 3',4'-dimethoxyvalerophenone (0.08 grams, 3.60 mmol) in a mixture of ethanol (25 milliliters) and water (5 milliliters) was added hydroxyamine hydrochloride (0.40 grams, 5.76 mmol) and sodium acetate (0.59 grams, 7.20 mmol) in water (5 milliliters). The solution was refluxed for two days. Reaction progress was monitored by TLC (20%, ethyl acetate/hexane, UV) and was complete after 2 days. The reaction was allowed to cool to ambient temperature and the ethanol was removed *in vacuo* to afford an oil/aqueous mixture. The mixture was extracted with methylene chloride. The dried extracts were concentrated *in vacuo* to afford 0.93 grams of crude product as a yellow oil. The crude product was purified by flash chromatography (silica gel, 20%, ethyl acetate/hexane) to afford 0.56 grams of product as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.23-8.01(br s , 1H), 7.30-7.05(m , 2H), 6.93-6.81(m , 1H), 3.91(s , 3H), 3.90(s , 3H), 2.84-2.70(m , 2H), 1.74-1.31(m , 4H), 0.93(t , J = 7.2 Hz , 3H); ^{13}C NMR ($CDCl_3$) δ 159.6, 150.1, 148.9, 128.5, 119.3, 110.6, 108.9, 55.9, 28.7, 25.6, 22.9, 13.8.

c) 1-(3',4'-Dimethoxyphenyl)pentylamine

To an N_2 flushed solution of 3',4'-dimethoxyvalerophenone oxime (0.5 grams, 2.1 mmol) in glacial acetic acid (10 milliliters) was added 0.1 grams of 5% Pd/C. The mixture was treated with 60 psi of H_2 in a Parr Type Shaker for 24 hours. The catalyst was filtered off through celite and the filtrate was concentrated *in vacuo* to afford a yellow oil. The oil was taken up in water, the pH was adjusted to 12 using a saturated solution of sodium carbonate, and extracted with methylene chloride. The organic extract was dried over magnesium sulfate and concentrated to afford 0.41 grams (87%) of product as a yellow oil : ^{1}H NMR ($CDCl_3$) δ 6.91-6.76(m , 3H), 3.98-3.78(m , 1H), 3.89(s , 3H), 3.87(s , 3H), 1.94-

0.78(m , 11H).

d) **1-Phthalimido-1-(3',4'-dimethoxyphenyl)pentane**

To a stirred solution of 1-(3',4'-dimethoxyphenyl)pentylamine (0.3 grams, 1.34 mmol) and sodium carbonate (0.15 grams, 1.45 mmol) in a mixture of water (10 milliliters) and acetonitrile (10 milliliters) was added N-carbethoxyphthalimide (0.29 grams, 1.34 mmol). The resulting solution was stirred for 3 hours at room temperature, the acetonitrile was evaporated and a two phase mixture resulted. The organic phase was extracted into methylene chloride, dried over magnesium sulfate and concentrated to afford 0.41 grams of crude product as an oil. The crude product was purified by flash chromatography (silica gel, 30% ethyl acetate/hexane) to afford 0.18 grams (38%) of the product as an oil : ^{1}H NMR ($CDCl_3$) δ 7.88-7.63(m , 4H), 7.20-7.07(m , 2H), 6.82-6.76(m , 1H), 5.34-5.18(m , 1H), 3.89(s , 3H), 3.85(s , 3H), 2.66-2.43(m , 1H), 2.40-2.17(m , 1H), 1.50-1.20(m , 2H), 0.96-0.81(m , 3H). ^{13}C NMR ($CDCl_3$) δ 1.68.5, 148.8, 148.5, 133.8, 132.5, 131.9, 123.1, 120.6, 111.6, 110.8, 55.9, 55.8, 55.0, 30.9, 29.2, 22.3, 13.9.

Example 7

1-Phthalimido-1-(3',4'-dimethoxyphenyl)-2-propylpentane.

a) **3',4'-Dimethoxy-2-propylvalerophenone.** 3',4'-Dimethoxyacetophenone (9.91 grams, 55 mmol) was added over 20 minutes to a cooled (0°C) stirred solution of lithium diisopropylamide (28.9 milliliters, 2M, 57.8 mmol). After an additional 5 minutes the solution was cooled to -78°C and 1-iodopropane (10.73 milliliters, 110 mmol) was rapidly added. The solution was allowed to slowly warm to room temperature and stirring was continued for 3 days. Reaction progress was monitored by TLC (30%, ethyl acetate/ hexane, UV) and an equilibrium had been reached after three days between starting

material (Rf = 0.15), monoalkylated product (Rf = 0.32) and dialkylated product (Rf = 0.42). The reaction was treated with water (60 milliliters), ethyl acetate (100 milliliters) and a saturated solution of sodium bicarbonate (100 milliliters). The organic layer was separated and washed successively with 5% HCl (100 milliliters) and saturated aqueous sodium bicarbonate (100 milliliters). The organic layer was dried over magnesium sulfate and concentrated to afford 15.17 grams of crude product as an orange oily liquid. The crude product was purified by flash chromatography (silica gel, 20% ethyl acetate/hexane) to afford 3.68 (25%) of the dialkylated product (3',4'-dimethoxy-2-propylvalerophenone) as a yellow solid and 1.01 grams (8%) of the monoalkylated product (3',4'-dimethoxyvalerophenone) as a yellow oily liquid: mp 55.5-56.5°C, ^{1}H NMR ($CDCl_3$) δ 7.67 - 7.54(m , 2 H), 6.96 - 6.86(m , 1 H), 3.95(s, 3 H), 3.93(s , 3 H), 3.52 - 3.36(m , 1 H), 1.86 - 1.17(m , 8 H), 0.96 - 0.80(m , 6 H). ^{13}C NMR ($CDCl_3$) δ 203.4, 143.1, 149.1, 131.0, 122.6, 110.3, 109.9, 56.0, 55.9, 45.1, 35.1, 20.9, 14.3.

b) 3',4'-Dimethoxy-2-propyl-valerophenone oxime.

To a stirred solution of 3',4'-dimethoxy-2-propylvalerophenone (2.64 grams, 10 mmol) in a mixture of ethanol (45 milliliters) and water (10 milliliters) was added hydroxyamine hydrochloride (1.11 grams, 16 mmol) and sodium acetate (1.64 grams, 20 mmol) in water (10 milliliters). The solution was refluxed for 1 week. Reaction progress was monitored by TLC (30%, ethyl acetate/hexane, UV) and had reached an equilibrium after 1 week. The reaction was allowed to cool to ambient temperature and the ethanol was removed *in vacuo* to afford an oil/aqueous mixture which was extracted with methylene chloride, dried over magnesium sulfate and concentrated *in vacuo* to afford 2.93 grams of crude product as a yellow oil. The crude product was purified by flash chromatography (silica gel, 30%, ethyl acetate/ hexane) to afford 1.28 grams (46%) of product as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.10-6.75(m , 3H), 3.78-3.96(m , 6H), 3.49-3.31(m , 0.5H), 2.65-2.50(m , 0.5H), 1.91-1.19(m , 8H), 1.01-0.81(m , 6H). ^{13}C NMR ($CDCl_3$) δ 162.5, 161.5, 149.5, 149.0, 148.6, 129.4, 125.9, 120.2, 111.2, 110.6, 110.5, 55.9, 55.8, 45.1, 38.9, 34.8, 21.3, 20.5, 14.2.

c) **1-(3',4'-Dimethoxyphenyl)-2-propylpentylamine**

To an N_2 flushed solution of 3',4'-dimethoxy-2-propyl-valerophenone (1.0 grams, 3.6 mmol) in glacial acetic acid (20 milliliters) was added 0.2 grams of 5% Pd/C. The mixture was treated with 60 psi of H_2 in a Parr Type Shaker for 24 hours. Reaction progress was monitored by TLC (30% ethyl acetate / hexane, UV) some starting material remained after 24 hours. A further 0.4 grams of 10% Pd/C was added and the mixture was treated with 60 psi of H_2 in a Parr Type Shaker for 24 hours. The catalyst was filtered off through celite and the filtrate was concentrated to afford a yellow oil. The oil was taken up in water, the pH was adjusted to 12 using a saturated solution of sodium carbonate, and extracted with methylene chloride. The organic extract was dried over magnesium sulfate and concentrated *in vacuo* to afford 0.51 grams (57%) of product as a yellow oil : ^{1}H NMR ($CDCl_3$) δ 6.91-6.74(m , 3H), 3.95-3.78(m , 1H), 3.89(s , 3H), 3.87(s , 3H), 1.67-0.75(m , 17H).

d) **1-Phthalimido-1-(3',4'-dimethoxyphenyl)-2-propylpentane.**

To a stirred solution of 1-(3',4'-dimethoxyphenyl)-2-propylpentylamine (0.40 grams, 1.60 mmol) and sodium carbonate (0.18 grams, 1.72 mmol) in a mixture of water (5 milliliters) and acetonitrile (10 milliliters) was added N-carbethoxyphthalimide (0.35 grams, 1.60 mmol). The resulting solution was stirred for 2.5 hours at room temperature, the acetonitrile was evaporated and a two phase mixture resulted. The organic phase was extracted into methylene chloride, dried over magnesium sulfate and concentrated *in vacuo* to afford 0.6 grams of crude product as an oil. The crude product was purified by flash chromatography (silica gel, 25% ethyl acetate/hexane) to afford 0.25 grams of the product as an oil which after a few days solidified. The white solid was dried *in vacuo* (60 °C , < 1 mm) to afford 0.24 grams of pure product as a white solid: mp 100-101°C; ^{1}H NMR ($CDCl_3$) δ 7.84-7.59(m , 4H), 7.27-7.02(m , 2H), 6.81-6.68(m , 1H), 5.01(d , J = 12 Hz , 1H), 3.89(s , 3H), 3.84(s , 3H), 3.17-2.98(m , 1H), 1.49-0.66(m , 14H). ^{13}C NMR ($CDCl_3$) δ 168.5, 148.7, 148.4, 133.8, 131.9, 131.8, 123.1, 121.6, 112.0, 110.7, 58.9, 55.9, 55.7, 36.2, 31.9, 31.8, 18.7, 18.1, 14.6, 14.3.

Anal. Calcd. for $C_{24}H_{29}NO_4$. Theoretical : C ,72.87; H , 7.40 ; N , 3.54. Found : C,72.70; H ,7.40; N ,3.51.

Example 8

Tablets, each containing 50 milligrams of active ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)

active ingredient	50.0 grams
lactose	50.7 grams
wheat starch	7.5 grams
polyethylene glycol 6000	5.0 grams
talc	5.0 grams
magnesium stearate	1.8 grams
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the talc, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 milliliters of water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 9

Tablets, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)

active ingredient	100.0 grams
lactose	100.0 grams
wheat starch	47.0 grams
magnesium stearate	3.0 grams

All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to 100 milliliters of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 10

Tablets for chewing, each containing 75 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)	
active ingredient	75.0 grams
mannitol	230.0 grams
lactose	150.0 grams
talc	21.0 grams
glycine	12.5 grams
stearic acid	10.0 grams
saccharin	1.5 grams
5% gelatin solution	q.s.

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. The active ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whol

is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

Example 11

Tablets, each containing 10 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)

active ingredient	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 12

Gelatin dry-filled capsules, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 capsules)

active ingredient	100.0 grams
microcrystalline cellulose	30.0 grams
sodium lauryl sulphate	2.0 grams
magnesium stearate	8.0 grams

The sodium lauryl sulphate is sieved into the active ingredient through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 milligrams each into size 0 (elongated) gelatin dry-fill capsules.

Example 13

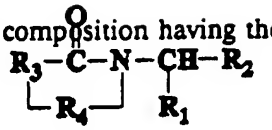
A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

active ingredient	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water	to 2500.0 milliliters

The active ingredient is dissolved in 1000 milliliters of water and filtered through a microfilter. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare dosage unit forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 milligrams of active ingredient).

What is claimed is:

Claim 1. A composition having the formula:



wherein,

R^1 is (*i*) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (*ii*) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iii) benzyl or benzyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, or (iv) -Y-Ph where Y is a straight, branched, or cyclic alkyl of 1 to 12 carbon atoms and Ph is phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo;

R^2 is -H, a branched or unbranched alkyl of 1 to 10 carbon atoms, phenyl, pyridyl, heterocycle, $-CH_2$-Aryl, or $-CH_2$-heterocycle.

R^3 is i) ethylene, ii) vinylene, iii) a branched alkylene of 3 to 10 carbon atoms, iv) a branched alkenylene of 3 to 10 carbon atoms, v) cycloalkylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy,

carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, vi) cycloalkenylene of 4 to 9 carbon atoms unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo, or vii) *o*-phenylene unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo;

R^4 is -CX, or $-CH_2-$; and,

X is O or S.

Claim 2. The composition of claim 1 wherein R^4 is -CO-.

Claim 3. The composition of claim 2 wherein R^1 is 3,4-dimethoxyphenyl.

Claim 4. The composition of claim 2 wherein R^2 is methyl.

Claim 5. The composition of claim 2 wherein R^2 is ethyl.

Claim 6. The composition of claim 2 wherein R^2 is hydrogen.

Claim 7. The composition of claim 2 wherein R^2 is phenyl.

Claim 8. The composition of claim 2 wherein R^2 is methyl.

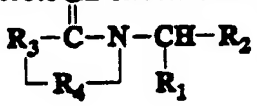
Claim 9. The composition of claim 2 wherein R^2 is 1-propyl-butane

Claim 10. The composition of claim 2 wherein R^2 is methoxyphenyl.

Claim 11. The composition of claim 2 wherein R^3 is *o*-phenyl.

Claim 12. The method of reducing levels of TNFα in a mammal which comprises administering thereto an effective amount of a compound of claim 1.

Claim 13. The method of reducing levels of TNFα in a mammal which comprises administering thereto an effective amount of a compound of the formula:



wherein,

R^1 is (*i*) straight, branched, or cyclic alkyl of 1 to 12 carbon atoms, (*ii*) phenyl or phenyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, (iii) benzyl or benzyl substituted with one or more substituents each selected independently of the other from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo, or (iv) -Y-Ph where Y is a straight, branched, or cyclic alkyl of 1 to 12 carbon atoms and Ph is phenyl or phenyl substituted with one or more substituents each selected independently of the other from

nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, alkyl of 1 to 10 carbon atoms, alkoxy of 1 to 10 carbon atoms, or halo;

R^2 is -H, a branched or unbranched alkyl of 1 to 10 carbon atoms, phenyl, pyridyl, heterocycle, $-CH_2$-Aryl, or $-CH_2$-heterocycle.

R^3 is *o*-phenylene unsubstituted or substituted with 1 to 2 substituents each selected independently from nitro, cyano, trifluoromethyl, carbethoxy, carbomethoxy, carbopropoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, substituted amino, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, or halo; and,

R^4 is -CO- or $-CH_2$-.

Claim 14. The method of inhibiting TNFα-activated retrovirus replication in a mammal which comprises administering thereto an effective amount of a compound according to claim 1.

Claim 15. The method of inhibiting TNFα-activated retrovirus replication in a mammal which comprises administering thereto an effective amount of a compound according to claim 2.

Claim 16. A pharmaceutical composition comprising an amount of a compound according to claim 1 effective upon single or multiple dosage to inhibit TNFα.

Claim 17. A pharmaceutical composition comprising an amount of a compound according to claim 2 effective upon single or multiple dosage to inhibit TNFα.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/15384

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/48 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOLOGICAL & PHARMACEUTICAL BULLETIN (OF JAPAN), vol. 17, no. 9, September 1994 UTICAL SOCIETY OF JAPAN JP, pages 1313-1315, K. SASAKI ET AL. 'Enhancement of 12-o-tetradecanoylphorbol-13-acetate-induced tumor factor alpha production by phenethylphthalimide analogs' see page 1313 --- -/--	1-17

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 1996	25.03.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 95/15384

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BIOLOGICAL & PHARMACEUTICAL BULLETIN (OF JAPAN), vol. 18, no. 9, September 1995 UTICAL SOCIETY OF JAPAN JP, pages 1228-1233, K. SASAKI ET AL. 'Benzylphthalimides and phenethylphthalimides with Thalidomide-like activity on the production of tumor necrosis factor alpha' see table 2	1-17
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH Frankfurt DE, see BRN=5086688 & TETRAHEDRON LETTERS, vol. 29, no. 22, 1988 OXFORD GB, pages 2639-2642, M.P. DOYLE ET AL.	1-3,6
X	DATABASE CROSSFIRE Beilstein Informationssysteme GmbH Frankfurt DE, see BRN=1471607 & FARMACO ED. SCI., vol. 31, 1976 pages 489-490, GHISLANDI ET AL.	1,2,5,7
X	DATABASE CROSSFIRE Beilstein Informationssysteme Frankfurt DE, see BRN=236720 & CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 38, no. 7, 1990 TOKYO JP, pages 2060-2062, Y. KATO ET AL.	10

1

INTERNATIONAL SEARCH REPORT

In tional application No.
PCT/US95/15384

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12 -15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Although the search was limited to compounds according to claim 11, thousands of novelty destroying compounds were found. Only a few examples of such compounds have been cited in the search report.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.